UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/611,949	07/06/2000	David M. Margolis	0184-0001CIP	6524

7590 01/24/2005

SHANKS & HERBERT
TransPotomac Plaza
Suite 306
1033 N. Fairfax St.
Alexandria, VA 22314

EXAMINER	
GUZO, DAVID	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 01/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/611,949	MARGOLIS ET AL.	
	Examiner	Art Unit	
	David Guzo	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *1-10 and 12-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 July 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Notice to Comply with Sequence Rules.

Detailed Action

Applicant's election without traverse of Group XII, claim 11 in the reply filed on 12/30/04 is acknowledged.

Claims 1-10 and 12-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 12/30/04.

Sequence Rules

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicants have not filed a Sequence Listing for this application.

Applicant must comply with the sequence rules, 37 CFR 1.821 - 1.825. Applicant is requested to return a copy of the attached Notice to Comply with the reply. Any reply to this Office Action which does not include complete compliance with the Sequence Rules will be considered non-responsive. The nature of the non-compliance with the Sequence Rules has not precluded an examination of the application on the merits, the results of which are communicated below.

35 USC 112, 1st Paragraph Rejections

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 11 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants claim a method of treating or preventing latent HIV infection in a human subject in need of such treatment or prevention comprising administering to the subject (a) an amount of an inhibitor of an HDAC1-recruiting activity of YYI, said amount being effective to inhibit repression of HIV transcription, and (b) a therapeutically effective amount of one or more anti-viral drugs selected from the group consisting of AZT, 3TC, ddI, ddC, saquinavir, indinavir, ritonavir, nelfinavir, nevirapine and efavirenz.

It appears that applicants' invention involves the following concept. The treatment of HIV using combinations of anti-retroviral drugs (such as AZT, indinavir, ddI, etc.), known as highly active anti-retroviral therapy (HAART), is effective in reducing plasma viremia to undetectable levels. However, replication competent HIV can still be isolated from latently infected $CD4^+$ T cells and suspension of HAART results in viral rebound in patients. Applicants disclosed that HIV gene activation is suppressed, in part, by recruitment of HDAC1 to the viral LTR by the transcription factor YY1 and inhibition of this recruitment can activate HIV gene expression *in vitro*. Applicants'

administration of an agent (in combination with anti-retroviral drugs) that activates HIV gene expression in latently infected cells by interfering with the HDAC1 recruiting activity of YY1 is believed to result in latently infected cells dying from cytopathic effects or immune effector mechanisms while the anti-retroviral agents would prevent new rounds of infection caused by the new virions produced by the activation of the virus in the latently infected cells.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor, but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

1) Unpredictability of the art. The art in this area involves the treatment or prevention of latent HIV infection in patients. This art must be considered extremely unpredictable. With regard to the **prevention** of latent HIV infection, the art is not only unpredictable but is also non-existent. With regard to use of agents which are designed to activate HIV expression in latently infected cells in combination with HAART to treat patients, the art is unpredictable. For example, use of IL-2 to activate HIV gene expression in latently infected cells (in combination with antiretroviral agents) to treat latent HIV infection in patients "...has failed to demonstrate a consistent diminution of the pool of latently infected cells or of viral rebound following cessation of therapy..."

(Demonte et al., Biochem. Pharmacology, 2004, Vol. 68, pp. 1231-1238, p. 1236). See also Chun et al., Nature, 1999, Vol. 401, pp. 874-875 for disclosure of failure of attempts to purge latent HIV infection by administering IL-2 and HAART. Indeed, IL-2 appears to activate HIV gene expression by down-modulating the binding activity of YY1 and LSF to the HIV LTR (See Bovolenta et al., J. Immunol., 1999, Vol. 163, pp. 6892-6897). It is noted that an inhibition of binding of YY1 and LSF to the viral LTR would have the same effect on HIV gene activation as inhibiting binding of the HDAC1 to the YY1 since binding of YY1, LSF and HDAC1 to the HIV LTR are apparently required to repress HIV gene expression. Since the art indicates that this approach has failed to treat latent HIV infection, it is unclear how applicants' method would overcome the failures with this approach which are noted in the cited art. It is also noted that recently some researchers have contemplated treatment of latent HIV infections by use of HDAC inhibitors (HDACi) in combination with HAART (See Demonte et al., 2004, cited above); however, this proposal is speculative, remains untried in patients and indeed, Demonte et al. concludes that inclusion of HDACi in treatments merely "deserves further investigations" (p. 1236).

2) State of the art. The art in this area at the time of applicants' invention was nil.

3) Number of working examples. Applicants present no working examples of the claimed invention.

4) Amount of guidance provided by applicants. Applicants present no specific guidance on the dosages of any specific agent which inhibits a HDAC1 recruiting activity of YY1, no specific guidance on the duration of treatment which would be

sufficient to purge the patient of latent HIV, no guidance on how to prevent latent infection of cells by HIV, etc. Since YY1 is an important transcription factor involved in numerous normal biochemical signal pathways, it is important that administration of any inhibitors of YY1 activity not result in deleterious effects in the patient. Applicants present no guidance on how the skilled artisan would choose the appropriate inhibitor of YY1-HDAC1 binding as well as the appropriate dosages and treatment schedules so as avoid negative effects on the patient.

5) Scope of the invention. The scope of the invention involves treatment or prevention of HIV infection (involving any strain of HIV) in human subjects.

6) Nature of the invention. The invention involves the prevention of latent HIV infection, something which has not previously been demonstrated in the art. The invention also involves treatment of latent HIV infection by methodologies (involving disruption of YY1-HDAC1-LSF binding to HIV LTRs) which have not previously been successful.

7) Level of skill in the art. The level of skill in the art is high; however, given the lack of success in treating or preventing latent HIV infection in patients, given the absence of working examples provided by applicants, given the unpredictability of the HIV treatment or prevention art, given the poorly developed state of the art, and given the lack of guidance on specific dosages (and duration of treatment) of inhibitors of YY1 recruitment of HDAC1 to be administered to patients, it must be considered that the skilled artisan would have needed to have practiced essentially trial and error experimentation in order to attempt to practice the claimed invention.

Given the above analysis of the factors which the courts have determined are critical to enablement of a claimed invention, it must be considered that the skilled artisan would have needed to have conducted undue and excessive experimentation in order to practice the claimed invention.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo, Ph.D., whose telephone number is (571) 272-0767. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D., can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David Guzo
January 24, 2005

DAVID GUZO
PRIMARY EXAMINER